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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 311/39, A61K 31/18

A1

(11) International Publication Number: WO 98/33769

(43) International Publication Date: 6 August 1998 (06.08.98)

(21) International Application Number: PCT/GB98/00342

(22) International Filing Date: 3 February 1998 (03.02.98)

(30) Priority Data:
A165/97 3 February 1997 (03.02.97) AT

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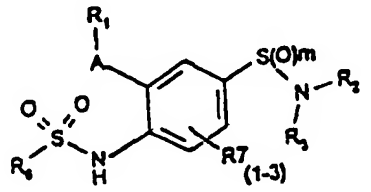
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUBSTITUTED DERIVATIVES OF BENZOSULPHONAMIDES AS INHIBITORS OF THE ENZYME CYCLOOXYGENASE II

(57) Abstract

The present application relates to compounds of formula (I) wherein A represents oxygen, sulfur or –NH–, m is 0–2, and R_1, R_2, R_3, R_6 and R_7 have the meanings given in the specification, to a process for their preparation, as well as to their use in the inhibition of cyclooxygenase II.



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SUBSTITUTED DERIVATIVES OF BENZOSULPHONAMIDES AS INHIBITORS OF THE ENZYME CYCLOOXYGENASE II

The invention relates to novel compounds having anti-inflammatory activity.

Prostaglandins play a decisive role in inflammatory processes and inhibition of the formation of prostaglandin, especially the formation of PGG_2, PGH_2 and PGE_2, is the common characteristic of compounds with anti-inflammatory activity. The known non-steroidal anti-inflammatory drugs (NSAIDs), which reduce prostaglandin-induced pain and swelling during the inflammation process, also influence prostaglandin-regulated processes which do not accompany inflammation processes. For this reason, most known NSAIDs cause undesirable side-effects in high doses, often even dangerous ulcers, especially stomach ulcers, gastric haemorrhages and such like. For this reason, the therapeutic potential of these compounds is decisively reduced.

Most known NSAIDs prevent the formation of prostaglandins by the inhibition of enzymes in human arachidonic acid metabolism, especially by inhibiting the enzyme cyclooxygenase (COX). The enzyme cyclo-oxygenase II (COX-2) is an enzyme of human arachidonic acid metabolism which has only been discovered recently. (Proc. Natl. Acad. Sci. USA, 89, 7384, 1992). COX-2 is induced by cytokines or endotoxins.

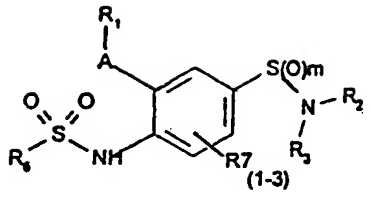
The discovery of this inducible enzyme, which plays a decisive role in inflammation processes, offers the possibility of searching for selectively effective compounds with an anti-inflammatory activity, which inhibit the inflammation process in a more effective manner without influencing other prostaglandin-regulated processes, and thus having fewer and fewer serious side-effects.

5-methylsulphonamide-1-indanones, which inhibit the enzyme cyclooxygenase II and which can therefore be utilised during the treatment of inflammation processes, are known from WO 94/13635. The potential of these compounds, and their side-effects, have not yet been fully clarified. Furthermore, these known compounds dissolve poorly, and thus have decisive disadvantages with regard to their formulation and application. Hence there is still a demand for new cyclooxygenase II-selective compounds, which, due to their effect and side-effect profiles, are safe and efficient in applications for the treatment of inflammatory processes.

The objective of the present invention was thus the provision of new non-steroidal anti-inflammatory drugs (NSAIDs), which selectively inhibit cyclooxygenase II (COX-2) and thus have fewer and fewer serious undesired side effects.

This objective could be unexpectedly solved by the provision of new derivatives of benzenesulphonic acid. As a result of their selective effect on the enzyme Cyclooxygenase II, these new compounds have excellent anti-inflammatory, analgesic, antipyretic and anti-allergic effects, but without the extremely undesirable side-effects of known anti-inflammatory agents.

The subject matter of the invention are thus compounds of formula I



wherein

A denotes oxygen, sulphur or NH,
R_1 is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy,
R_2 and R_3, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$-X,

or

R_2 and R_3, together with the N- atom denotes a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$-X,

X denotes halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, -CN, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$,
n denotes a whole number from 0 to 6,
R_6 denotes a straight-chained or branched alkyl group with 1-10 C- atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or

heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy,
R_7 denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, or a polyfluoroalkyl group,
R_4 and R_5, independently from one another, denote hydrogen, alkyl, aralkyl or aryl, and
m denotes a whole number from 0 to 2,
and the pharmaceutically-acceptable salts thereof.

A denotes oxygen, sulphur or NH.

R_1 denotes an optionally unsaturated alkyl or alkyloxyalkyl group, each with 1-12 C-atoms in the alkyl chain, for example a methyl, an ethyl, a propyl, an isopropyl, a butyl, an isobutyl, a tertiary-butyl, a pentyl, an isopentyl, a hexyl or an isohexyl group and the like, or for example unsaturated alkyl groups such as ethenyl, butenyl, or alkyoxyalkyl groups such as methoxymethyl, ethoxymethyl and the like. These groups can optionally be substituted by halogen, for example F, Cl or Br, by alkoxy, oxo or cyano. Furthermore, R_1 can denote a cycloalkyl group, for example a cyclohexyl or a cyclopentyl group, an aryl group, for example a phenyl group, or heteroaryl group, for example a furyl, thienyl, thiazolyl, imidazolyl, thiadiazolyl, pyridyl, pyridinyl or pyrazolyl group. These groups can optionally be mono- or polysubstituted or mixed substituted by halogen, for example Cl, F, Br or by CF_3 or alkyl with 1-4 C-atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tertiary-butyl or alkoxy with 1-4 C-atoms, for example methoxy, ethoxy, propoxy or butoxy or cyano.

R_2 and R_3, independently from one another, denote hydrogen, an optionally polyfluorized alkyl group with 1-6 C-atoms, for example methyl, an ethyl, a propyl, an isopropyl, a butyl, an isobutyl, a tertiary-butyl, a pentyl, an isopentyl, a hexyl or an isohexyl group, a CF_3 group or C_2F_5, an aralkyl group with 1-4 C-atoms in the alkyl chain, for example a benzyl group, an ethylphenyl group, an aryl group, for example a phenyl group or a heteroaryl group, for example a pyridyl group, a pyridazinyl group, a thienyl group, a thiazolyl group or an isothiazolyl group.

R_2 and R_3 can also, independently from one another, denote a group $-(CH_2)_n-X$, whereby X is halogen, $-NO_2$, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, and n is a whole number from 0 to 6.

Examples of such groups are halogen alkyl groups, for example chloromethyl, chloroethyl, the group -CN, nitroalkyl groups, for example nitromethyl, nitroethyl or cyanoalkyl groups, for example cyanomethyl, cyanopropyl, cyanohexyl, a hydroxy group or hydroxyalkyl groups, for example hydroxymethyl, hydroxyethyl, hydroxypropyl bishydroxymethyl-methyl. Other examples are alkoxy groups such as methoxy, ethoxy, propoxy, butoxy, pentoxy, the groups methyloxy-ethyl, ethyloxy-methyl, carboxylic acid groups such as ethoxycarbonyl, methoxycarbonyl, acetyl, propionyl, butyryl, isobutyryl groups and their alkyl-, aralkyl- or aryl esters, carbamoyl groups, oxycarbonyloxy groups, for example the ethoxycarbonyloxy group, carboxymide acid groups, thiocarboxy groups and such like.

R_4 and R_5 denote, independently of one another, hydrogen, alkyl with 1-6 C-atoms, aralkyl with 1-4 C-atoms in the alkyl chain, for example benzyl, ethylphenyl or aryl,

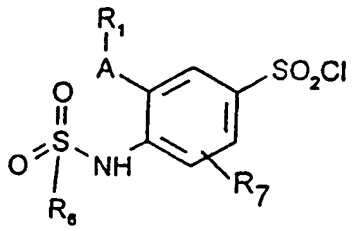
for example phenyl.

Furthermore, R_2 and R_3, together with the N-atom, can form a 3- to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $-(CH_2)_n-X$, whereby X denotes halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, and n is a whole number from 0 to 6.

Examples of such rings are the morpholyl group, the aziridinyl group, the azetidinyl group, the pyridyl group, the pyrazolyl group, the thiazolyl group and such like.

R_6 denotes a straight chain or branched alkyl group with 1-10 C-atoms, for example methyl, an ethyl, a propyl, an isopropyl, a butyl, an isobutyl, a tertiary-butyl, a pentyl, an isopentyl, a hexyl or an isohexyl group or such like, a CF_3 group or C_2F_5, an aralkyl group with 1-4 C-atoms in the alkyl chain, for example a benzyl group, an ethylphenyl group, an aryl group, for example a phenyl group or a heteroaryl group, for example a pyridyl group, a pyridazinyl group, a thienyl group, a thiazolyl group or an isothiazolyl group or a heteroaralkyl group, for example. These groups can, for example, be mono- or polysubstituted or mixed substituted by halogen, for example Cl, F or Br, or alkoxy, for example methoxy, ethoxy and such like, by $-NO_2$, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$.

The compounds, according to the invention, can be prepared by reacting a compound of formula III



III

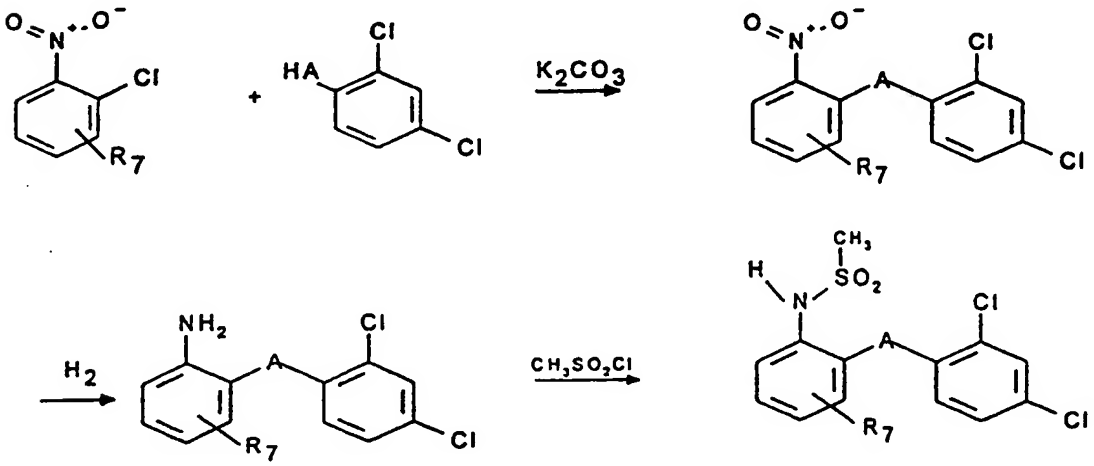
with a compound of formula IV

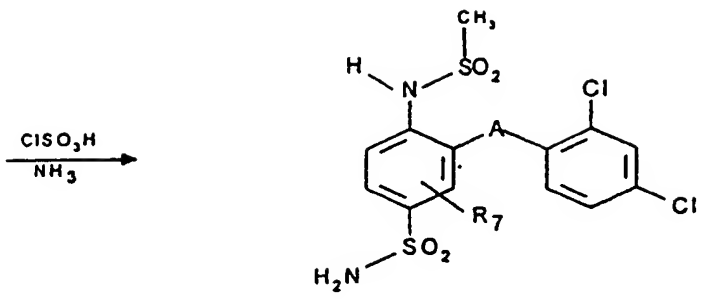
HNR_2R_3 IV

or a salt thereof.

This reaction preferably takes place in the presence of a diluent or solvent which is inert under reaction conditions, for example dioxan, tetrahydrofuran or such like. The reaction temperature is approximately -10°C up to the reflux temperature of the solvent or diluent preferably -10°C up to room temperature.

The starting compounds of formula III can, for example, be prepared according to the following reaction scheme or by other methods familiar to the skilled person.





The compounds of formula I, obtained as described above, are acidic or basic compounds and can be converted in the usual manner with inorganic or organic bases or acids respectively into their pharmaceutically-acceptable salts. The salt formation can, for example, be carried out by adding at least an equivalent quantity of the desired base or acid to a compound of formula I in a suitable solvent, such as for example water, acetone, acetonitrile, benzene, dimethylformamide, dimethyl-sulphoxide, chloroform, dioxan, methanol, ethanol, hexanol, ethylacetate, or in an aliphatic ether, for example diethylether, or mixtures of such solvents, being mixed well, and after completion of salt formation the precipitated salt is filtered off, lyophilised or the solvent is distilled off in a vacuum. If necessary, the salts can be recrystallised after isolation.

Pharmaceutically-acceptable salts are those with inorganic acids, such as for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid or nitric acid, or with organic acids such as citric acid, tartaric acid, maleic acid, fumaric acid, succinic acid, malic acid, methanesulphonic acid, aminosulphonic acid, acetic acid, benzoic acid and such like.

Pharmaceutically-acceptable salts are e.g. metallic salts, especially alkaline metal or alkaline-earth metal salts such as sodium, potassium, magnesium or calcium salts. Other pharmaceutical salts are, for example, easily-crystallising ammonium salts. These are derived from ammonia or organic amines, such as mono-, di- or tri-lower-(alkyl, cycloalkyl or hydroxyalkyl)-amines, lower alkylene diamines or hydroxy- or aryl-lower-alkyl ammonium bases e.g. methylamine, diethylamine, triethylamine, ethylenediamine, tris-(hydroxymethyl)-aminomethane, benzyltrimethylammonium hydroxide and such like.

The new compounds have good solubility and, as a result of their selective effect on the enzyme cyclooxygenase II, they have excellent anti-inflammatory, analgesic, antipyretic and antiallergic effects, but without the extremely undesirable side-effects of known anti-inflammatory agents.

As a result of this pharmacological characteristic, the new compounds can be used, individually or in combination with other effective substances in the form of common galenic preparations as medicaments for the treatment of disorders or diseases which can be treated or healed by inhibition of the enzyme cyclooxygenase II.

These disorders or diseases embrace pain, fever and inflammations of various types, for example rheumatic fever, symptoms associated with influenza or other viral infections, head and joint pains, toothache, sprains, distortions, neuralgia, muscle inflammation, joint inflammation, joint membrane inflammation, arthritis, rheumatoid arthritis, other rheumatic inflammation form degenerative manifestations, for example osteoarthritis, gouty arthritis, stiffening of the joints, spondylitis,

bursitis, burns and injuries.

The invention thus relates to pharmaceutical preparations which contain the compounds of formula I, according to the invention, or their salts, alone or mixed with other therapeutically-active substances, as well as common galenic adjuvant and/or carrier substances or diluents.

The compounds according to the invention can be orally applied in the form of tablets or capsules which contain a single dose of the compound together with adjuvant substances and diluents such as maize starch, calcium carbonate, dicalcium phosphate, algenic acid, lactose, magnesium stearate, primogel or talcum. The tablets are manufactured in the traditional manner by granulating the contents and pressing into shape, the capsules by filling hard gelatine capsules of suitable size.

A further application form of the compounds, according to the invention, are suppositories which contain adjuvant substances such as beeswax derivatives, polyethylene glycol or polyethylene glycol derivatives, linoleic acid or linoleic acid esters, together with a single dose of the compound and which are rectally administered.

The compounds, according to the invention, can also be parenterally applied, for example by intramuscular, intravenous or subcutaneous injection. For parenteral application, it is best that they are used in the form of a sterile aqueous solution, which can contain other dissolved materials such as tonic agents, agents for standardization of the pH value, preservatives and stabilisers. Distilled water can be added to the compounds and the pH value can be adjusted to between 3 and 6 by using, for example, citric acid, lactic acid or

hydrochloric acid. Sufficiently-dissolved materials, such as dextrose or salt solutions, can be added in order to isotonically set the solution. In addition, preservatives such as p-hydroxybenzoate, and stabilisers such as EDTA, can be added to give the solution a sufficient shelf-life and stability. The solution obtained in this way can then be sterilised and decanted into sterile ampoules of a suitable size so that they contain the desired volume of solution. The compounds, according to the invention, can also be applied by infusion of a parenteral formulation as described above.

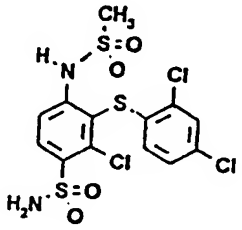
Furthermore, the compounds, according to the invention, can be formulated for topical or transdermal application with suitable adjuvant and/or carrier substances, emulsifiers, tensides and/or diluents, e.g. vaseline, olive oil, peanut oil, sesame seed oil, soya oil, water, glycols, cetylstearyl esters, triglycerides, cetaceum, miglyol and such like into ointments, creams, gels or plasters, or for example formulated into powder with talcum.

For oral application with humans, it is accepted that the daily dosage of a compound according to the invention, will lie in the range of 0.01 to 1000 mg per day for a typical adult patient of 70 kg. Hence tablets or capsules can usually contain 0.003 to 300 mg of active compound, for example 0.1 to 50 mg, for oral application up to three times per day. With parenteral administration, the dose can lie in the range of 0.001 to 1000 mg per 70 kg per day, for example approximately 5 mg.

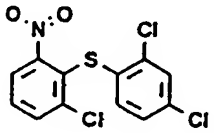
Example 1: 3-(2,4-Dichlorophenylthio)-2-chloro-4-methylsulphonylamino-benzosulphonamide

$C_{13}H_{11}Cl_3N_2O_4S_3$

FW: 461.79 $gmol^{-1}$

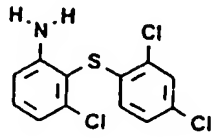


a) 3-chloro-2-(2,4-dichlorophenylthio)-nitrobenzene



Sodium carbonate (13.8g) is added to a solution of 1,2-dichloro-3-nitrobenzene (19.2g) and 2,4-dichlorothiophenol (17.9g) in xylene (250 ml), and the resulting mixture is heated for 5 hours at reflux temperature. The precipitate is separated by filtration, washed with xylene and the combined organic phases are concentrated. The resultant residue is mixed with petroleum ether and stirred for 1 hour at room temperature. Following this, the crystalline material is suction filtered and washed with petroleum ether, and any remaining solvent is removed in a vacuum. Yield: 25.6g of colourless crystals (76.6%).

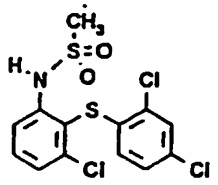
b) 3-chloro-2-(2,4-dichlorophenylthio)-aniline



A solution of 3-chloro-2-(2,4-dichlorophenylthio)-nitrobenzene (10.04g) in dioxan (100 ml) is mixed with Raney-nickel (5g). Following this, the mixture is shaken for 3 hours at room temperature and 3 bar hydrogen pressure in a Parr apparatus. The catalyst is removed by filtration. The filtrate is concentrated in a vacuum and the resulting residue is brought to constant weight in a vacuum. Yield 9.01g (98.6%) of colourless oil.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 151.1, 141.4, 133.4, 131.9, 131.8, 131.3, 129.3, 127.5, 126.6, 119.4, 113.5, 111.2.

c) 3-chloro-2-(2,4-dichlorophenylthio)-N-methyl-sulphonyl-aniline

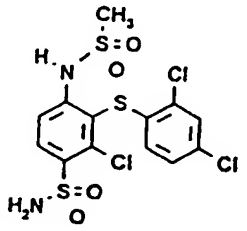


3-chloro-2-(2,4-dichlorophenylthio)-aniline (8.96g) is dissolved in pyridine (300 ml). Methane sulphochloride (4.56 ml) is added dropwise to this solution and the resulting mixture is stirred for 12 hours at room temperature. Following this, the mixture is emptied onto iced water, acidified with concentrated hydrochloric acid. The resulting mixture is extracted 3 times with methylene chloride (each 200 ml). The combined organic phases are dried (Na_2SO_4), filtered and the filtrate is concentrated in a vacuum. The resulting

residue is dissolved in methanol, mixed with a sodium methylate solution in methanol (29.7%, 50 ml) and is stirred for 12 hours. The clear solution is acidified with concentrated hydrochloric acid, brought to room temperature, diluted with water (200 ml). The resulting precipitate is suction filtered, washed with water and dried. Yield: 10.69g (95.0%).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 142.1, 142.0, 132.8, 132.63, 132.58, 131.8, 129.9, 127.9, 127.4, 125.9, 118.4, 116.9, 40.0.

d) 2-chloro-3-(2,4-dichlorophenylthio)-4-methyl-sulphonylamino-benzosulphonamide



Chlorosulphonic acid (3.69 ml) is dissolved in methylene chloride (100 ml), cooled to 0°C and added dropwise to a solution of 3-chloro-2-(2,4-dichlorophenylthio)-N-methylsulphonyl-aniline (10.6g) in methylene chloride (100 ml). After an hour, phosphorus pentachloride (23.07g) is added and the mixture is stirred for one more hour at 0°C. Following this, the solution is brought to room temperature and stirred for a further one hour. The precipitate is suction-filtered and the filtrate is emptied onto an iced water mixture. The organic phase is separated, dried (Na_2SO_4), filtered and concentrated in a vacuum. The resulting residue is dissolved in dioxan (80 ml) and is added dropwise to a mixture of dioxan (80 ml) and concentrated aqueous ammonia (120 ml), cooled to 0°C. The resulting mixture is stirred for a further 2 hours at room temperature. Following this, it is diluted with water (250 ml),

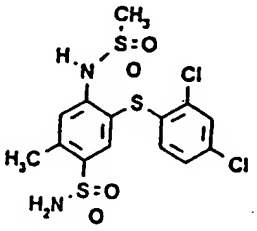
acidified with concentrated hydrochloric acid and cooled to room temperature. The resulting crystals are suction-filtered, washed with ethanol and dried in a vacuum. Yield: 6.74g (59.0%).

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 145.5, 138.7, 133.5, 131.8, 131.1, 131.1, 129.3, 128.3, 127.5, 123.5, 120.4, 41.4.

The following compounds were prepared analogously to Example 1:

Example 2: 5-(2,4-dichlorophenylthio)-2-methyl-4-methylsulphonylamino-benzosulphonamide

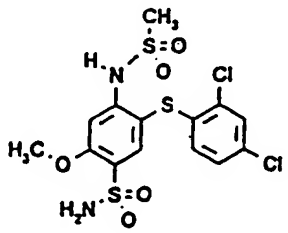
$C_{14}H_{14}Cl_2N_2O_4S_3$
FW: 441.38 gmol^{-1}



Mp: 250-253°C
^{13}C-NMR (d_6-DMSO, 100 MHz): δ 153.8, 138.2, 137.8, 137.3, 134.0, 130.1, 129.0, 128.6, 128.2, 127.0, 120.5, 113.2, 41.0, 20.8.

Example 3: 5-(2,4-dichlorophenylthio)-2-methoxy-4-methylsulphonylamino-benzosulphonamide

$C_{14}H_{14}Cl_2N_2O_5S_3$
FW: 457.38 gmol^{-1}



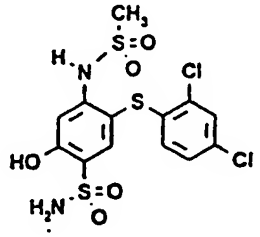
Mp: 258-262°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 158.2, 145.2, 136.2, 135.4, 131.3, 131.1, 129.3, 128.8, 128.3, 11.3, 106.4, 56.6, 41.0.

Example 4: 5-(2,4-dichlorophenylthio)-2-hydroxy-4-vinylsulphonylamino-benzosulphonamide

$C_{13}H_{12}Cl_2N_2O_4S_3$

FW: 443.35 gmol^{-1}

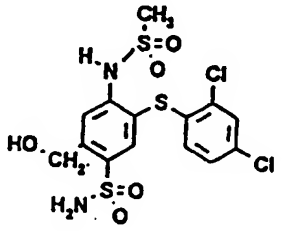


^{13}C-NMR (d_6-DMSO, 100 MHz): δ 157.6, 145.0, 137.0, 135.9, 130.9, 130.8, 129.2, 128.3, 128.0, 127.2, 109.6, 108.7, 56.2, 18.7.

Example 5: 5-(2,4-dichlorophenylthio)-2-hydroxymethyl-4-methylsulphonylamino-benzosulphonamide

$C_{14}H_{14}Cl_2N_2O_5S_3$

FW: 457.38 gmol^{-1}



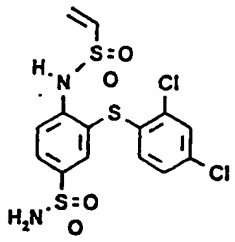
Mp: 185-187°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 138.0, 136.6, 135.5, 134.3, 133.7, 133.2, 130.9, 129.5, 128.6, 128.3, 128.2, 127.2, 41.1, 34.3.

Example 6: 3-(2,4-dichlorophenylthio)-4-vinylsulphonyl-amino-benzosulphonamide

$C_{14}H_{12}Cl_2N_2O_4S_3$

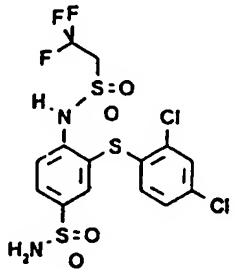
FW: 439.36 $gmol^{-1}$



Mp: 180-182°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 132.2, 140.3, 136.7, 134.3, 132.9, 132.8, 130.8, 129.7, 128.6, 128.3, 127.8, 127.0, 125.5, 40.0.

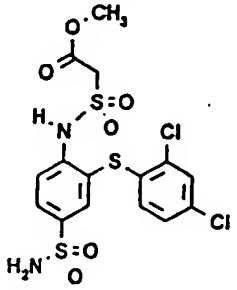
Example 7: 3-(2,4-dichlorophenylthio)-4-(2,2,2-trifluoro-ethyl)sulphonylamino-benzosulphonamide



Mp: 210-213°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 143.0, 139.2, 134.7, 133.3, 133.0, 132.3, 130.1, 130.0, 129.8, 128.6, 127.1, 126.7, 123.7, 120.9, 55.45, 55.15, 54.85, 54.55.

Example 8: 3-(2,4-dichlorophenylthio)-4-methoxy-carbonylmethylsulphonylamino-benzosulphonamide



Mp: 182-185°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 163.5, 142.4, 140.3, 134.3, 132.9, 132.8, 132.4, 130.8, 129.7, 128.6, 127.1, 125.8, 57.5, 52.8.

EXAMPLE A

Human COX-2 Test

Cells of a human monocytoid cell line were stimulated with lipopolysaccharide (LPS) (incubator at 37°C, 5% CO_2-enriched atmosphere and almost 100% atmospheric humidity), in order to induce COX-2. Following this, the culture medium (RPMI 1640, enriched with 10% FCS, 2 mM glutamine, 10000 U/ml penicillin, 10 ng/ml streptomycin and 1 mM pyruvate) is refreshed and potential inhibitor substances of cyclooxygenase-II, dissolved in culture medium or in phosphate-buffered saline or in some other solvent compatible with cell cultures, are added and then incubated for half an hour as described above. Arachidonic acid is added by pipette and incubation is carried out for a further 15 minutes. The culture supernatant of the cells is removed and its content of products of cyclooxygenase metabolism (e.g. Prostaglandin E2, Prostaglandin F_{1a}, Thromboxane B_2) is measured by ELISA.

EXAMPLE B

Human COX-1 Test

Inhibition of the arachidonic acid-induced aggregation of washed human thrombocytes was used as a test system for an estimation of the inhibition of cyclooxygenase-I. A thrombocyte suspension at 37°C was added to the test substances 2 minutes before addition of the arachidonic acid (10 μM final concentration) and the aggregation course was recorded via an aggregometer. With the assistance of a concentration-effect curve, the concentration of test substance was determined at which 50% aggregation was measured (IC50).

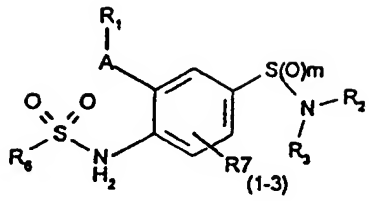
The results of both tests, and also the selectivity determined from the tests, are given in Table 1.

Table 1

Compound according to Example	COX I IC50 μM	COX II IC50 μM	COX I/COX II
1	25	0.10	250
6	20	0.10	200

Claims

1. Compounds of formula I



wherein
A denotes oxygen, sulphur or NH,
R_1 denotes an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy,
R_2 and R_3, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$-X, or
R_2 and R_3, together with the N- atom denotes a 3- to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$-X,
X denotes halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, -CN, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$,
n is a whole number from 0 to 6,
R_6 denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group, which may optionally be substituted by halogen or alkoxy,
R_7 denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl

group with 1-6 C-atoms, which may optionally be mono- or polysubstituted by halogen, $-NO_2$, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, or a polyfluoroalkyl group,
R_4 and R_5, independently from one another, denote hydrogen, alkyl, aralkyl or aryl, and
m is a whole number from 0 to 2,
and the pharmaceutically-acceptable salts thereof.

2. Compounds of formula I according to claim 1, wherein R_7 denotes halogen, hydroxy or an alkyl or alkoxycarbonyl group with 1-4 C-atoms which may optionally be substituted by halogen or hydroxy.

3. Compounds of formula I according to one of claims 1 or 2, wherein R_1 may optionally be an unsaturated alkyl or alkyloxyalkyl group which may optionally be mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano.

4. A pharmaceutical composition containing as an active ingredient at least one compound of general formula I according to claim 1.

5. The use of compounds of formula I according to claim 1 as a means of treatment and alleviation of diseases or disorders which can be healed or alleviated by inhibition of the enzyme cyclooxygenase II.

6. The use of compounds of formula I according to claim 1 as a means for treatment or alleviation of inflammatory processes.

7. The use of compounds of formula I according to claim 1 as a means for treatment of pain.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 98/00342

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/39 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DE 195 33 644 A (NYCOMED ARZNEIMITTEL GMBH) 13 March 1997 see the whole document ---	1-7
P,X	WO 97 03953 A (HAFSLUND NYCOMED PHARMA ;BLASCHKE HEINZ (AT); KREMMINGER PETER (AT) 6 February 1997 see the whole document ---	1-7
A	WO 94 13635 A (MERCK FROSST CANADA INC ;FORD HUTCHINSON ANTHONY W (CA); KENNEDY B) 23 June 1994 cited in the application -----	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 1998	09. 04. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Janus, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna .ial application No.
PCT/GB 98/ 00342

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5-7
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5-7 can be regarded as relating to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internationa pplication No
PCT/GB 98/00342

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19533644 A	13-03-97	NONE	
WO 9703953 A	06-02-97	AU 6361096 A	18-02-97
WO 9413635 A	23-06-94	US 5604260 A	18-02-97
		AU 5621594 A	04-07-94
		CA 2151235 A	23-06-94
		EP 0673366 A	27-09-95
		JP 8504408 T	14-05-96

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 403/02, A61K 31/415 — A1

(11) International Publication Number: **WO 98/41519**

(43) International Publication Date: 24 September 1998 (24.09.98)

(21) International Application Number: PCT/US98/05352

(22) International Filing Date: 18 March 1998 (18.03.98)

(30) Priority Data:

60/040,808	18 March 1997 (18.03.97)	US
60/043,060	4 April 1997 (04.04.97)	US

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BENDER, Paul, Elliot [US/US]; 504 Lilac Lane, Cherry Hill, NJ 08003 (US). CHRISTENSEN, Siegfried, Benjamin, IV [US/US]; 2301 Cherry Street #4–M, Philadelphia, PA 19103 (US).

(74) Agents: SIMON, Soma, G. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406–0939 (US).

(54) Title: NOVEL CANNABINOID RECEPTOR AGONISTS

(57) Abstract

Novel pyrazole derivatives are provided which are cannabinoid receptor agonists.

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NOVEL CANNABINOID RECEPTOR AGONISTS

This application claims benefit from U.S. application 60/040,808 filed March 18, 1997 and 60/043,060 filed April 4, 1997.

FIELD OF THE INVENTION

The present invention relates to novel pyrazole derivatives, pharmaceutical compositions containing these compounds and their use as cannabinoid peripheral receptor agonists.

BACKGROUND OF THE INVENTION

Cannabinoids are a specific class of psychoactive compounds present in Indian cannabis (*Cannabis sativa*), including about sixty different molecules, the most representative being cannabinol, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of cannabis dates back to the ancient dynasties of China, where, 5,000 years ago, cannabis was used for the treatment of asthma, migraine and some gynaecological disorders. These uses later became so established that, around 1850, cannabis extracts were included in the US Pharmacopaeia and remained there until 1947.

Cannabinoids are known to cause different effects on various systems and/or organs, the most important being on the central nervous system and on the cardiovascular system. These effects include alterations in memory and cognition, euphoria, and sedation. Cannabinoids also increase heart rate and vary systemic arterial pressure. Peripheral effects, such as bronchial dilation, immunomodulation, and downregulation of inflammation have also been observed. The capability of cannabinoids to reduce intraocular pressure and to affect respiratory and endocrine systems is also well documented. See e.g. L.E. Hollister, Health Aspects of Cannabis, Pharmacological Reviews, Vol. 38, pp. 1-20, (1986). More recently, it was found that cannabinoids suppress the cellular and humoral immune responses and exhibit antiinflammatory properties. Wirth et al., Antiinflammatory Properties of Cannabichrome, Life Science, Vol. 26, pp. 1991-1995, (1980).

In spite of the foregoing benefits, the therapeutic use of cannabis is controversial, due to its psychoactive effects. Although work in this field has been ongoing since the 1940's, evidence indicating that the peripheral effects of cannabinoids are directly mediated, and not secondary to a CNS effect, has been limited by the lack of receptor

characterization, the lack of information concerning an endogenous cannabinoid ligand and, until recently, the lack of receptor subtype selective compounds.

The first cannabinoid receptor was found to be mainly localized in the brain, and, only to a lesser extent, in peripheral tissues. In view of its mRNA localization, it was designated the central receptor ("CB1"). See Matsuda et al., "Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA," Nature, Vol. 346, pp. 561-564 (1990. The second cannabinoid receptor ("CB2") was localized primarily to the spleen with low expression in the CNS, and was postulated to modulate the non psychoactive effects of the cannabinoids. See Munro et el., "Molecular Characterization of a Peripheral Receptor for Cannabinoids," Nature, Vol. 365, pp. 61-65 (1993).

The foregoing indications and the preferential localization of the CB2 receptor in the immune system suggest a specific role of CB2 in modulating the immune and antiinflammatory response of cannabinoids.

The role of CB2 in immunomodulation, inflammation, osteoporosis, cardiovascular, renal and other disease conditions is currently under examination. In light of the fact that cannabinoids act on receptors capable of modulating different functional effects, and in view of the low homology between CB2 and CB1, the importance of developing a class of drugs selective for the CB2 receptor subtype is evident. The natural or synthetic cannabinoids currently available do not fulfill this function because they are active on both receptor subtypes.

Based on the foregoing, there is a need for compounds which are capable of selectively activating the peripheral cannabinoid receptor. Thus, CB2 agonists offer a unique approach toward the pharmacotherapy of immune disorders, inflammation, osteoporosis, renal ischemia and other pathophysiological conditions.

Recently, some compounds have been prepared and reported capable of acting as agonists on both cannabinoid receptors. For example, use of derivatives of dihydroxypyrrole-(1,2,3-d,e)-1,4-benzoxazine in the treatment of glaucoma and the use of derivatives of 1,5-diphenyl-pyrazole as immunomodultors or psychotropic agents in the treatment of various neuropathologies, migraine, epilepsy, glaucoma, etc are known. See U.S. Patent No. 5,112,820 and EP 576357, respectively. However, because these compounds are active on both the CB1 and CB2 receptor, they can lead to serious psychoactive effects. Also recently described are indole derivatives which are reported to selectively bind to CB2 over CB1 receptors. See Michel Gallant et al, Bioorganic & Medicinal Chemistry Letters, 6(19), pp. 2263-2268 (1996).

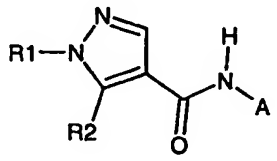
SUMMARY OF THE INVENTION

The present invention provides novel pyrazole derivatives represented by Formula (I) and pharmaceutical compositions containing these compounds, and their use as CB2 receptor agonists which are useful in the treatment of a variety of diseases including but not limited to immune disorder, inflammation, osteoporosis, psoriasis, eczema and renal ischemia.

The present invention further comprises a method for activating CB2 receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are represented by structural Formula (I):



Formula (I)

wherein:

A is selected from the group consisting of 1-adamantyl, 2-adamantyl, 3-noradamantyl, and 1,1,3,3-tetramethylbutyl;

R_2 is selected from the group consisting of 2-(4-morpholino)ethoxy, 2-(diallylamino)ethoxy, 2-, 3-, or 4-pyridylmethoxy, 2-(diethylamino)ethoxy, 1-methylpiperidinyl-2-methoxy, benzyloxy and 4-substituted benzyloxy; where the substituent is selected from the group consisting of hydrogen, fluoro, chloro, methoxy, methylthio, and nitro; and

R_1 is selected from the group consisting of C_{1-6} alkyl, 3- or 4-biphenyl, unsubstituted or substituted by halo, 1-naphthyl, benzyl, phenethyl, phenyl, monosubstituted phenyl, wherein the substituent is selected from the group consisting of hydrogen, C_{1-4} alkyl, fluoro, chloro, bromo, methoxy, trifluoromethyl, and nitro, or disubstituted phenyl where the substituents are, independently, selected from the group consisting of fluoro, chloro, or methyl.

Also included in the present invention are pharmaceutically-acceptable salt complexes. Preferred salt complexes include hydrochloride, hydrobromide, citrate, tartrate, malate, maleate, lactate,fructose 1,6-diphosphate, phosphate, succinate, sulfate, aspartate, adipate, methanesulfonate, lauryl sulfate, diguaiacyl phosphate, diacetyl sulfate, glutamate, gluconate, and edetate.

All alkyl and alkoxy groups may be straight or branched. The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

As used herein, "allyl" means $-CH_2=CH-CH_2-$.

In preferred compounds of the present invention, A is 1- adamantyl, 2-adamantyl, or 3-noradamantyl; R_2 is selected from the group consisting of 2-(4-morpholino)ethoxy, 4-pyridylmethoxy,1-methylpiperidinyl-2-methoxy, benzyloxy, and 4-fluoro-benzyloxy, and R_1 is phenyl, benzyl, or 4-monosubstituted phenyl wherein the substitutent is selected from the group consisting of C_{1-4} alkyl, fluoro, chloro, methoxy , and trifluoromethyl.

In more preferred compounds of the present invention, A is 1-adamantyl; R_2 is selected from the group consisting of 2-(4-morpholino)ethoxy, 4-pyridylmethoxy, and 1-methylpiperidinyl-2-methoxy; and R_1 is phenyl, benzyl, or 4-monosubstituted phenyl wherein the substitutent is selected from the group consisting of C_{1-4} alkyl, fluoro, chloro, and methoxy.

In even more preferred compounds of the present invention, R_2 is 2-(4-morpholino)ethoxy, and R_1 is phenyl; or 4-monosubstituted phenyl wherein the substituent is C_{1-4} alkyl.

Preferred compounds useful in the present invention are selected from the group consisting of:

N-(1-Adamantyl)-1-(4-isopropylphenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(4-(2,6-dichlorophenyl)phenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(2-Adamantyl)-1-(4-fluorophenyl)-5-(4-pyridylmethoxy)pyrazole-4-carboxamide,

N-(3-Noradamantyl)-1-(4-chlorophenyl)-5-(1-methylpiperidinyl-2-methoxy)pyrazole-4-carboxamide,

N-(1,1,3,3-Tetramethylbutyl)-5-(4-fluorobenzyloxy)-1-(4-methoxyphenyl)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(2,5-difluorophenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(2,3-dimethylphenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(1-Adamantyl)-5-(2-(4-morpholino)ethoxy)-1-(phenethyl)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-benzyl -5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-benzyl-5-(2-diallylaminoethoxy)pyrazole-4-carboxamide,

N-(2-Adamantyl)-1-(4-bromophenyl)-5-(4-methylthiobenzyloxy)pyrazole-4-carboxamide,

N-(3-Noradamantyl)-5-(benzyloxy)-1-(4-chlorophenyl)pyrazole-4-carboxamide,

N-(1,1,3,3-Tetramethylbutyl)-5-(4-chlorobenzyloxy)-1-(1-naphthyl)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(4-biphenyl)-5-(2-pyridylmethoxy)pyrazole-4-carboxamide,

N-(2-Adamantyl)-5-(4-methoxybenzyloxy)-1-(4-trifluorophenyl)pyrazole-4-carboxamide,

N-(3-Noradamantyl)-1-(4-nitrophenyl)-5-(3-pyridylmethoxy)pyrazole-4-carboxamide,

N-(1,1,3,3-Tetramethylbutyl)-1-(1-hexyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(4-fluorophenyl)-5-(4-pyridylmethoxy)pyrazole-4-carboxamide,

N-(2-Adamantyl)-5-(4-fluorobenzyloxy)-1-(4-methoxyphenyl)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(4-chlorophenyl)-5-(1-methylpiperidinyl-2-methoxy)pyrazole-4-carboxamide; and

N-(1-Adamantyl)-1-phenyl-5-(4-pyridylmethoxy)pyrazole-4-carboxamide.

More preferred compounds useful in the present invention are selected from the group consisting of:

N-(1-Adamantyl)-1-(4-isopropylphenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(2-Adamantyl)-1-(4-fluorophenyl)-5-(4-pyridylmethoxy)pyrazole-4-carboxamide,

N-(3-Noradamantyl)-1-(4-chlorophenyl)-5-(1-methylpiperidinyl-2-methoxy)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-benzyl-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,

N-(2-Adamantyl)-5-(4-fluorobenzyloxy)-1-(4-methoxyphenyl)pyrazole-4-carboxamide,

N-(3-Noradamantyl)-5-(benzyloxy)-1-(4-chlorophenyl)pyrazole-4-carboxamide,

N-(1-Adamantyl)-1-(4-fluorophenyl)-5-(4-pyridylmethoxy)pyrazole-4-carboxamide,

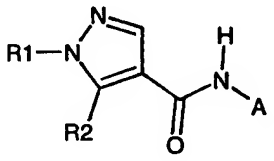
N-(1-Adamantyl)-1-(4-chlorophenyl)-5-(1-methylpiperidinyl-2-methoxy)pyrazole-4-carboxamide, and

N-(1-Adamantyl)-1-phenyl-5-(4-pyridylmethoxy)pyrazole-4-carboxamide.

The most preferred compound useful in the present invention is:

N-(1-Adamantyl)-1-(4-isopropylphenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide.

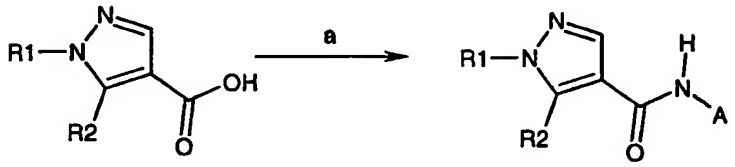
The present invention provides compounds of Formula (I):



Formula (I)

which can be prepared by processes described in Schemes 1 and 2 below.

Scheme 1

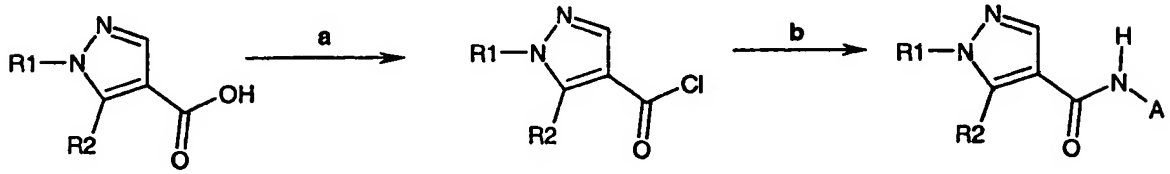


Formula (I)

a) HOBT, EDC, TEA, DMF, A-NH_2.

In Scheme 1, above, the pyrazole-5-carboxylic acids are converted to the N-alkyl pyrazole-5-carboxamides by standard amide coupling chemistry (by reacting with 1-hydroxybenzotriazine hydrate ("HOBT"),1-(3-dimethylaminopropyl)-3-ethylcarbodiimide ("EDC"), triethylamine ("TEA"), and 1-adamantane amine hydrochloride, in dimethylformamide ("DMF")).

Scheme 2



1 2 Formula (I)

a) thionyl chloride, b) methylene chloride, A-amine, $NaHCO_3$

An alternative and preferred process, shown in Scheme 2, above, consists of:

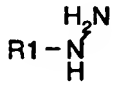
a) converting the pyrazole-5-carboxylic acid 1 to the pyrazole-5-carbonyl chloride 2 employing standard conditions (such as treating with thionyl chloride either neat or in the presence of an inert solvent, or with oxalyl chloride in a suitable solvent such as benzene in presence of a catalytic amount of N,N-dimethylformamide) followed by:

b) treating the acid chloride 2 in an inert solvent (e.g. chloroform, methylene chloride, toluene) with the required amine ($A\text{-}NH_2$) in the presence of a tertiary base (e.g. triethyl amine, or N-methylmorpholine) or an inorganic base (such as a metal bicarbonate eg sodium bicarbonate) in cold water to provide the Formula (I) compounds.

Formula (I) compounds wherein R_1 is 3- or 4-biphenyl are prepared by a process which comprises: reacting the corresponding Formula (I) compound wherein R_1 is 3-Br or 4-Br respectively with phenyl boronic acid in a suitable solvent (eg toluene-ethanol-water, 1,2-dimethoxyethane-water, tetrahydrofuran-water, or N,N-dimethylformamide-water) in the presence of a base (eg sodium carbonate, sodium bicarbonate, potassium carbonate, triethylamine) with 3 to 5 mole percent of a palladium derivative (eg palladium acetate, tetrakis(triphenylphosphine)palladium, or palladium acetate in the presence of bis(diphenylphosphino)butane) at 25 to 100 °C for 5 to 24 h.

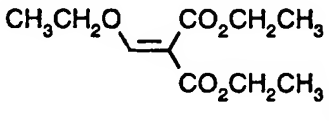
The pyrazole-5-carboxylic acids (1) can be prepared by a process which comprises:

a) reacting a hydrazine (3), wherein R_1 is as defined above,



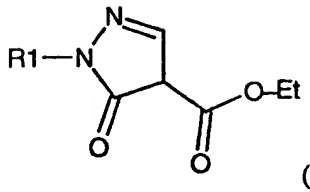
(3)

with diethyl ethoxymethylenemalonate (4)



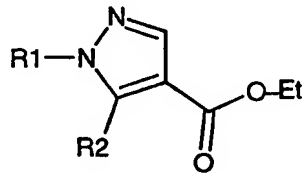
(4)

in the presence of a base such as potassium carbonate in aqueous solution to form an ester pyrazolone of Formula (5);



(5)

b) reacting the compound of Formula (5) above in a Mitsunobu reaction with an alcohol, R_2-OH (6), wherein R_2 is as defined above, in the presence of a tri-alkyl- or triaryl- phosphine and a dialkyl azodicarboxylate in a suitable solvent such as tetrahydrofuran, providing a compound of Formula (7);



(7)

c) and saponifying the Mitsunobu reaction product above, (7), with a base such as NaOH in a mixture of ethanol and water to afford the pyrazole-5-carboxylic acid (1).

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

As used herein, "modulator" means both antagonist and agonist. Preferably, the present modulators are agonists.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

In addition to the conditions listed hereinabove, the present compounds are useful for the treatment of diseases including but not limited to immunologically-mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus

erythematosus, psoriasis, eczema, multiple schlerosis, diabetes and thyroiditis. In addition, the present compounds modulate bone formation/resorption and are useful in the treatment of conditions including but not limited to ankylosing spondylitis, gout, arthritis associated with gout, osteoarthritis and osteoporosis.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parentarally, sub-lingually, dermally, transdermally, rectally, via inhalation or via buccal administration.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols,

gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of Formula(I) or a pharmaceutically acceptable salt thereof calculated as the free base. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula(I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

<u>Human CB2 Cannabinoid Receptor Binding Assay</u>

CB2 membranes are made from a polyclonal HEK 293 cell line stabily expressing the human CB2 receptor. The assay buffer comprises 50 mM Tris(pH7.4), 5mM MgCl2, 2.5 mM EDTA and 5 mg/ml Bovine Serium Albumin Fraction V fatty acid-free(Cal Biochem). Unless otherwise noted, all chemicals are from Sigma. Tritiated 5-(1,1-dimethylheptyl)-2-(5-hydroxypropyl)cyclohexyl)-1 alpha, 2beta, 5 alpha)-phenol([^{3}H]-CP55,940,103.4 Ci/mmol, 1mCi/ml) is purchased from DuPont NEN. Test compounds are

made by Medicinal Chemistry SmithKline Beecham Pharmacuticals and are dissolved in DMSO.

The ligand binding mixture contains 1.3-1.8nM [^{3}H]-CP55,940, 20 ug of CB2 membranes and 5 ul of each test compound in a total reaction volume of 150 ul of assay buffer. The final concentrations of compounds range from 1.00E-4 to 1.00E-10M; and the final DMSO concentration is 3.3%. The ligand binding mixtures are incubated in 96 deep well polypropylene microtiter plates for one hour at 30° C and terminated by rapid filtration (Brandel 96-well cell harvester) over GF/B filters treated with wash buffer(50 mM Tris, 0.5 mg/ml fatty acid-free BSA, pH7.4), and followed by five washes with 3 ml ice-cold buffer. The filters are air-dried and [^{3}H]-CP55,940 bound radioactivity is determined by liquid scintillation counting. Non-specific binding is determined in the presence of 1 uM CP55,940. The binding data is analyzed with the program GraphPad Prism. K_i values ranging from 1 nM to 10 uM are obtained for the compounds of the present invention.

cAMP Production In HEK293/CB2 Cells

To confirm agonist activity, the following test is conducted.

Polyclonal HEK293 cells stabily expressing human CB2 receptor are maintained in EMEM media supplemented with Earl's salts, L-glutamine, 10% FBS, and 0.5mg/ml G418 sulfate. 200µL of cell suspension (25,000-50,000 cells/well) are added to a 96 well plate pre-treated with dilute Matrigel (Collaborative Biomedical Products: diluted 1/50 with PBS and treated for 1 hr at room temperature) and incubated at 37 °C for three days in a 5% CO_2 incubator.

Growth media is removed from the assay plate and each well is rinsed with 200µL of cAMP assay buffer (EMEM media supplemented with Earl's salts, L-glutamine, 20mM Hepes, pH 7.4, 0.1mM $MgCl_2$ and 2mg/ml BSA Fraction V) and blotted dry. 50 µL of assay buffer are added to each well, followed by 100µL of 250 uM Zardaverine (a PDE 3-4 inhibitor diluted in assay buffer with 0.25% DMSO) and 50µL of the test compound (diluted in assay buffer containing 20mg/ml BSA and 1% DMSO). The cells are then incubated with compounds at room temperature for 30 minutes. To initiate cAMP production, 50 µL of 50 uM Forskolin (Calbiochem 344270 in assay buffer with 0.1% DMSO) is added and incubated for 15 minutes in a 37 °C incubator. The reaction is terminated by addition of 60uL 0.2N HCl and 0.2mM $CaCl_2$ and stored in a -80 °C freezer until cAMP determination.

For cAMP determinations 200μL of cell lysate is transferred to a 96 well round-bottom plate and 40μL of 0.1N NaOH and 0.1mM CaCl2 is added to neutralize the lysate. Following centrifugation at 2400 rpm for 5 minutes, 20-50μL of supernatant is assayed for cAMP using the Amersham EIA kit (RPN 225: unacetylated protocol). Using this procedure, forskolin stimulated cAMP levels range from 0.5-1.5 pmole per assay well and 5-15 pmole per original culture.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

EXAMPLE 1

Preparation of N-(1-Adamantyl)-5-(2-[4-morpholinyl]ethoxy)-1-(4-isopropylphenyl)pyrazole-4-carboxamide

To a stirred solution of 1-(4-isopropylphenyl)-5-(2-[4-morpholinyl]ethoxy)pyrazole-4-carboxylic acid (43 mg, 0.12 mmol) in dimethylformamide (1 mL) under an argon atmosphere, was added 1-hydroxybenzotriazole (16 mg, 0.12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (25 mg, 0.13 mmol), triethylamine (60 uL, 0.43 mmol) and 1-adamantanamine hydrochloride (25 mg, 0.13 mmol). The reaction mixture was stirred for 24 h at room temperature, heated to 70 °C for 2 h, and stirred for another 96 h at room temperature. The resulting mixture was treated with aqueous sodium carbonate, extracted with ethyl acetate, washed with water four times and dried over Na_2SO_4. The extract was concentrated *in vacuo* . This coupling was repeated on the same scale and the combined residue was purified by chromatography twice over silica gel eluting the first column with 2 to 3% methanol in chloroform, and the second with 30 to 40% ethyl acetate in chloroform to afford the title compound (7% yield, 8.5 mg) as a yellow powder, mp 132-134 °C. MS (ES) m/e 493.4 $[M+H]^+$.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

EXAMPLE 2

Inhalant Formulation

A compound of Formula (I), (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

EXAMPLE 3

Tablet Formulation

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Cpd of Form. I)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

EXAMPLE 4

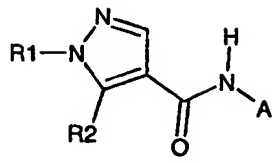
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula I

wherein:

A is selected from the group consisting of 1-adamantyl, 2-adamantyl, 3-noradamantyl, and 1,1,3,3-tetramethylbutyl;

R_2 is selected from the group consisting of 2-(4-morpholino)ethoxy, 2-(diallylamino)ethoxy, 2-, 3-, or 4-pyridylmethoxy, 2-(diethylamino)ethoxy, 1-methylpiperidinyl-2-methoxy, benzyloxy and 4-substituted benzyloxy;

where the substituent is selected from the group consisting of hydrogen, fluoro, chloro, methoxy, methylthio, and nitro; and

R_1 is selected from the group consisting of C_{1-6} alkyl, 3- or 4-biphenyl, unsubstituted or substituted by halo, 1-naphthyl, benzyl, phenethyl, phenyl, monosubstituted phenyl, wherein the substitutent is selected from the group consisting of hydrogen, C_{1-4} alkyl, fluoro, chloro, bromo, methoxy, trifluoromethyl, and nitro, or disubstituted phenyl where the substituents are independently selected from the group consisting of fluoro, chloro, or methyl; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein A is 1-adamantyl, 2-adamantyl or 3-noradamantyl; R_2 is selected from the group consisting of 2-(4-morpholino)ethoxy, 4-pyridylmethoxy,1-methylpiperidinyl-2-methoxy, benzyloxy, and 4-fluoro-benzyloxy, and R_1 is phenyl, benzyl, or 4-monosubstituted phenyl wherein the substitutent is selected from the group consisting of C_{1-4} alkyl, fluoro, chloro, methoxy , and trifluoromethyl.

3. A compound according to claim 2 wherein A is 1-adamantyl, R_2 is selected from the group consisting of 2-(4-morpholino)ethoxy, 4-pyridylmethoxy, and 1-methylpiperidinyl-2-methoxy, and R_1 is phenyl, benzyl, or 4-monosubstituted phenyl, wherein the substitutent is selected from the group consisting of C_{1-4} alkyl, fluoro, chloro, and methoxy.

4. A compound according to claim 3 wherein R_2 is 2-(4-morpholino)ethoxy, and R_1 is phenyl; or 4-monosubstituted phenyl wherein the substituent is C_{1-4} alkyl.

5. A compound according to claim 1 selected from the group consisting of:
N-(1-Adamantyl)-1-(4-isopropylphenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,
N-(2-Adamantyl)-1-(4-fluorophenyl)-5-(4-pyridylmethoxy)pyrazole-4-carboxamide,
N-(3-Noradamantyl)-1-(4-chlorophenyl)-5-(1-methylpiperidinyl-2-methoxy)pyrazole-4-carboxamide,
N-(1-Adamantyl)-1-benzyl-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide,
N-(2-Adamantyl)-5-(4-fluorobenzyloxy)-1-(4-methoxyphenyl)pyrazole-4-carboxamide,
N-(3-Noradamantyl)-5-(benzyloxy)-1-(4-chlorophenyl)pyrazole-4-carboxamide,
N-(1-Adamantyl)-1-(4-fluorophenyl)-5-(4-pyridylmethoxy)pyrazole-4-carboxamide,
N-(1-Adamanty)-1-(4-chlorophenyl)-5-(1-methylpiperidinyl-2-methoxy)pyrazole-4-carboxamide, and
N-(1-Adamantyl)-1-phenyl-5-(4-pyridylmethoxy)pyrazole-4-carboxamide.

6. A compound according to claim 5 which is:
N-(1-Adamantyl)-1-(4-isopropylphenyl)-5-(2-(4-morpholino)ethoxy)pyrazole-4-carboxamide.

7. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

8. A method of activating cannabinoid 2 receptors which comprises administering to a subject in need thereof, an effective amount of a compound of claim 1.

9. A method of treatment of diseases exhibiting a deficiency of cannabinoid receptor 2 function, comprising administering to a subject in need thereof an effective amount of a cannabinoid receptor 2 agonist according to claim 1.

10. A method of treating an immunologically-mediated inflammatory disease selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus, psoriasis, eczema, multiple sclerosis, diabetes and thyroiditis which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.

11. A method of treating a disease selected from the group consisting of ankylosing spondylitis, gout, gouty arthritis, osteoarthritis and osteoporosis which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.

12. A method of treating renal ischemia which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05352

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 403/02; A61K 31/415
US CL :544/140; 546/211, 275.1; 548/374.1; 514/236.5, 326, 341, 403
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/140; 546/211, 275.1; 548/374.1; 514/236.5, 326, 341, 403

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,217,523 A (DITRICH et al.) 08 June 1993, entire document	1-12
A	US 4,410,525 A (JARREAU et al.) 18 October 1983, entire document	1-12
A, P	US 5,750,721 A (GALLENKAMP et al.) 12 May 1998, entire document	1-12
A	US 4,298,749 A (PLATH et al.) 03 November 1981, entire document	1-12
A	US 4,226,877 A (ARENDSEN) 07 October 1980, entire document	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search 26 MAY 1998	Date of mailing of the international search report 16 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MATTHEW V. GRUMBLING Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/045

A1

(11) International Publication Number: WO 99/26612

(43) International Publication Date: 3 June 1999 (03.06.99)

(21) International Application Number: PCT/US98/24803

(22) International Filing Date: 20 November 1998 (20.11.98)

(30) Priority Data:

60/066,353	21 November 1997 (21.11.97)	US
60/068,085	19 December 1997 (19.12.97)	US

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

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(54) Title: NOVEL CANNABINOID RECEPTOR MODULATORS

(57) Abstract

Cannabinoid receptor modulators and methods of using them are provided.

FOR THE PURPOSES OF INFORMATION ONLY

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NOVEL CANNABINOID RECEPTOR MODULATORS

FIELD OF THE INVENTION

The present invention relates to the use of dialkyl phenol derivatives, and pharmaceutical compositions containing these compounds as cannabinoid peripheral receptor agonists.

Cannabinoids are a specific class of psychoactive compounds present in Indian cannabis (*Cannabis sativa*), including about sixty different molecules, the most representative being cannabinol, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of cannabis dates back to the ancient dynasties of China, where, 5,000 years ago, cannabis was used for the treatment of asthma, migraine and some gynaecological disorders. These uses later became so established that, around 1850, cannabis extracts were included in the US Pharmacopaeia and remained there until 1947.

Cannabinoids are known to cause different effects on various systems and/or organs, the most important being on the central nervous system and on the cardiovascular system. These effects include alterations in memory and cognition, euphoria, and sedation. Cannabinoids also increase heart rate and vary systemic arterial pressure. Peripheral effects related to bronchial constriction, immunomodulation, and inflammation have also been observed. The capability of cannabinoids to reduce intraocular pressure and to affect respiratory and endocrine systems is also well documented. See e.g. L.E. Hollister, Health Aspects of Cannabis, Pharmacological Reviews, Vol. 38, pp. 1-20, (1986). More recently, it was found that cannabinoids suppress the cellular and humoral immune response and have antiinflammatory properties. Wirth et al., Antiinflammatory Properties of Cannabichrome, Life Science, Vol. 26, pp. 1991-1995, (1980).

The initial demonstration of the existence of a cannabinoid receptor by radioreceptor binding occurred in 1988 followed by the cloning and characterization of the central acting receptor and peripheral receptor in 1990 and 1993 respectively.

Matsuda and collaborators identified and cloned a cannabinoid receptor belonging to the G-protein-coupled family of receptors, wherein CB1 is coupled to G1 to inhibit adenilate cyclase activity and to a partussis-sensitive G protein to regulate Ca^{2+} currents. The receptor is question was found to be mainly located in the brain, in neural cell lines, and, only to a lesser extent, at a peripheral level. In view of its location, it was called the Central Receptor ("CB1"). See Matsuda et al., "Structure of a Cannabinoid Receptor and

Functional Expression of the Cloned cDNA," Nature, Vol. 346, pp. 561-564 (1990). The discovery of this receptor led one to assume the existence of a specified endogenous ligand.

Subsequent research led to the isolation of a substance from the pig brain that was able to exert an antagonist action, i.e. bind to the cannabinoid central receptor in a competitive way. The substance was identified by structural investigation and by comparison with the synthetic product. It was found to be an amidic derivative of arachidonic acid, more particularly arachidonylethanolamide, later called anandamide. The pharmacological characterization of the molecule provided evidence that anandamide possessed a profile of activity which was similar to, though less potent than, delta-9-THC (tetrahydrocannabinol with a double bond in position 9), and was capable of mimicking the psychoactive effects thereof. This evidence led to the conclusion that anandamide was the endogenous ligand of the cannabinoid central receptor. See Felder, et el., "Anandamide, an Endogenous Cannabimimetic Eicosanoid, Binds to the Cloned Human Cannabinoid Receptor and Stimulates Receptor-mediated Signal Transduction," PNAS, Vol. 90, pp. 7656-7660 (1994).

Subsequent research led to the individuation of substances binding to CB1 receptor; these substances, grouped together into a class of amidic compounds, were denominated anadamides by the authors. Hanus, et el., "Two New Unsaturated Fatty Acids Ethanolamides in the Brain that Bind to the Cannabinoid Receptor," J. Med. Chem., Vol. 36, pp. 3032-3034, (1993).

The discovery that the ethanolamide of arachidonic acid, but not the ethanolamide of other acids which are biologically important and already endogenously present at the cerebral level (such as palmitic acid), is capable of functionally activating CB1 central receptor, brought about the subsequent identification of other amides of ethanolamine with highly unsaturated fatty acids which have an affinity to the CB1 receptor.

Its unique distribution led to the assumption of the existence of differentiated receptor sites. A second receptor for cannabinoids was cloned. This was named the Peripheral Receptor (CX5 or CB2). This receptor was identified in the spleen and macrophages/monocytes while being absent at the central level. It is assumed that this receptor mediates the non psychoactive effects of the cannabinoids. See Munro et el., "Molecular Characterization of a Peripheral Receptor for Cannabinoids," Nature, Vol. 365, pp. 61-65 (1993). In this connection there is evidence of the capacity of delta-9-THC to induce immunosuppressive effects. Recent experimental studies have demonstrated that delta-9-THC is capable of influencing the function of macrophage. Exposure to delta-9-

THC lowers the cytolytic action of activated macrophages, measured as synthesis, release and cytotoxicity of TNF-alpha. Because the macrophages release various molecules having a cytolytic potential, other than TNF-alpha, it is considered that they can represent a target for delta-9-THC. See Fischer-Stenger et el., "Delta9-tetrahydrocannabinol Inhibition of Tumor Necrosis Factor-alpha: Suppression of Post-translational Events," J. Pet., Vol. 267, Pp. 1558-1565 (1993).

The foregoing indications and the preferential massive localization of the CB2 receptor in the immuno system confirms that this receptor plays a specific role in mediating the immune and antiinflammatory response to stimuli of different nature, including bacterial and viral ones.

Research efforts also indicate that anandamide, the endogenous ligand for the CB1 central receptor, is capable of binding to the CB2 receptor with an affinity which is 30 fold lower to that of the central receptor. This probably implies the existence of a separate endogenous ligand up to now still unknown. Iversen, "Medical Uses of Marijuana?' Nature, Vol. 365, pp. 12-13 (1993).

As already mentioned, the therapeutic uses of cannabinoids as analgesics, antiemetics, anticonvulsives, antispastics, antiglaucoma and, more recently, antiinflammatory agents, is limited by the undesirable side effects and by the possibility of addiction and pharmacological tolerance.

The foregoing research advances have provided the impetus to investigate the role of the cannabinoid receptors in immunomodulation, inflammation, osteoporosis, cardiovascular, neurological, renal and other disease conditions. Cannabinoid receptor modulators thus offer a unique approach toward the pharmacotherapy of immunosuppression, neurological inflammation, arthritis, osteoporosis, renal ischemia, hematopoiesis, analgesia, neuropathic pain, pathologies related to improper small blood vessel vasodilation and other pathophysiological conditions.

Therefore novel, structurally distinct cannabinoid receptor agonists may find therapeutic uses as analgesics, antiemetics, anticonvulsives, antispastics, antiglaucoma, immunomodulators and antiinflammatory agents and not be limited by the undesirable side effects and by the possibility of addiction.

Recently, some compounds have been prepared, capable of acting as agonists on both the cannabinoid receptors. For example, use of derivatives of dihydroxypyrrole-(1,2, 3-d,e)-1,4-benzoxazine in the treatment of glaucoma and the use of derivatives of 1,

5-diphenyl-pyrazole as immunomodultors or psychotropic agents in the treatment of various neuropathologies, migraine, epilepsy, glaucoma, etc are known. See U.S. Patent No. 5,112,820 and EP 576357, respectively.

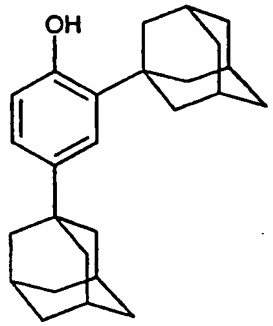
SUMMARY OF THE INVENTION

The present invention involves 2,4-bis-(1-adamantyl)phenol and its use as a cannabinoid receptor agonist, useful in the treatment of a variety of diseases associated with cardiovascular, renal, neurological and immune disorders, including but not limited to immunologically-mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple schlerosis, diabetis and thyroiditis; bone conditions including but not limited to ankylosing spondylitis, gout, arthritis associated with gout, osteoarthritis and osteoporosis.

The present invention further provides methods for agonizing cannabinoid receptors in an animal, including humans, which comprises administering to a subject in need of treatment an effective amount of the present compound.

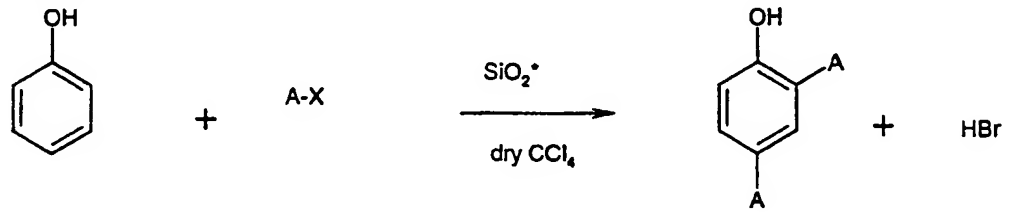
DETAILED DESCRIPTION OF THE INVENTION

The compound useful in the present methods is 2,4-bis-(1-adamantyl)phenol:



Also included in the present invention are pharmaceutically acceptable salt complexes. Preferred are the ethylene diamine, sodium, potassium and calcium salts.

The present compound can be prepared by the using the strategies provided hereinbelow as well as the specific example cited.



1 2 Formula I

wherein A-X represents 1-adamantyl halide, wherein the halide is chloride, iodide or preferably bromide.

Scheme 1

Formula I compounds are prepared by the process of Scheme 1 which comprises: heating a 1-adamantyl halide of Formula 2 with a phenol of formula 1 at 50 to 150 °C in a dry suitable solvent such as carbon tetrachloride, or dichloroethane for 10 to 48 h in the presence of a Lewis acid catalyst such as silica (activated by heating between 100 and 250 °C under vacuum for 1 to 24 h.).

In order to use the present compound or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

In addition to the conditions listed hereinabove, the present compound is useful for the treatment of diseases including but not limited to immunologically-mediated inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple schlerosis, diabetis and thyroiditis. In addition, the present compound modulates bone formation/resorption and is useful in the treatment of conditions including but not limited to ankylosing spondylitis, gout, arthritis associated with gout, osteoarthritis and osteoporosis.

The present compound and its pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, dermally, transdermally, rectally, via inhalation or via buccal administration.

Composition of the present compound and its pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for

preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil. for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises the present compound or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of Formula(I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of the present compound.

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of the present compound or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of the compound or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when the present compound is administered in accordance with the present invention.

The biological activity of the present compound is demonstrated by the following test:

CANNABINOID RECEPTOR BINDING ASSAY

Rat CB1 membranes (rCB1) are made from homogenized cerebellum, recombinant human CB1 membranes (hCB1) are obtained from Receptor Biology Inc. (Baltimore, MD), and human CB2 membranes (hCB2) are made from a polyclonal HEK 293 cell line stably expressing the human CB2 receptor. The assay buffer comprises 50 mM Tris(pH7.4), 5mM MgCl2, 2.5 mM EDTA and 5 mg/ml Bovine Serium Albumin Fraction V fatty acid-free(Cal Biochem). Unless otherwise noted, all chemicals are from Sigma. Tritiated 5-(1,1-dimethylheptyl)-2-(5-hydroxypropyl)cyclohexyl)-1 alpha, 2beta, 5 alpha)-phenol([^{3}H]-CP55,940,103.4 Ci/mmol, 1mCi/ml) is purchased from DuPont NEN. Test compounds are made by Medicinal Chemistry SmithKline Beecham Pharmacuticals and are dissolved in DMSO.

The ligand binding mixture contains 1.3-1.8nM [^{3}H]-CP55,940, 5 ul of each test compound in a total reaction volume of 150 ul of assay buffer and either 50 ug/ml of rCB1, 25 ug/ml hCB1, or 20 ug/ml hCB2 membranes. The final concentrations of compounds range from 1.00E-4 to 1.00E-10M; and the final DMSO concentration is 3.3%. The ligand binding mixtures are incubated in 96 deep well polypropylene microtiter plates for one hour at 30^o C and terminated by rapid filtration (Brandel 96-well cell harvester) over GF/B filters treated with wash buffer(50 mM Tris, 0.5 mg/ml fatty acid-free BSA, pH7.4), and followed by five washes with 3 ml ice-cold buffer. The filters are air-dried and [^{3}H]-CP55,940 bound radioactivity is determined by liquid scintillation counting. Non-specific binding is determined in the presence of 1 uM CP55,940. The binding data is analyzed with

the program GraphPad Prism. K_i values ranging from 1 nM to 10 uM are obtained for the compounds of the present invention.

cAMP PRODUCTION IN HEK293/CB2 CELLS METHODOLOGY

To confirm agonist activity, the following test is conducted.

Polyclonal HEK293 cells stably expressing human CB2 receptor are maintained in EMEM media supplemented with Earl's salts, L-glutamine, 10% FBS, and 0.5mg/ml G418 sulfate. 200 uL of cell suspension (25,000-50,000 cells/well) are added to a 96 well plate pre-treated with dilute Matrigel (Collaborative Biomedical Products: diluted 1/50 with PBS and treated for 1 hr at room temperature) and incubated at 37 °C for three days in a 5% CO_2 incubator.

Growth media is removed from the assay plate and each well is rinsed with 200 uL of cAMP assay buffer (EMEM media supplemented with Earl's salts, L-glutamine, 20mM Hepes, pH 7.4, 0.1mM $MgCl_2$ and 2mg/ml BSA Fraction V) and blotted dry. 50 uL of assay buffer are added to each well, followed by 100 uL of 250 uM Zardaverine (a PDE 3-4 inhibitor diluted in assay buffer with 0.25% DMSO) and 50 uL of the test compound (diluted in assay buffer containing 20mg/ml BSA and 1% DMSO). The cells are then incubated with compounds at room temperature for 30 minutes. To initiate cAMP production, 50 uL of 50 uM Forskolin (Calbiochem 344270 in assay buffer with 0.1% DMSO) is added and incubated for 15 minutes in a 37 °C incubator. The reaction is terminated by addition of 60uL 0.2N HCl and 0.2mM $CaCl_2$ and stored in a -80 °C freezer until cAMP determination.

For cAMP determinations 200 uL of cell lysate is transferred to a 96 well round-bottom plate and 40 uL of 0.1N NaOH and 0.1mM CaCl2 is added to neutralize the lysate. Following centrifugation at 2400 rpm for 5 minutes, 20-50µL of supernatant is assayed for cAMP using the Amersham EIA kit (RPN 225: unacetylated protocol). Using this procedure, forskolin stimulated cAMP levels range from 0.5-1.5 pmole per assay well and 5-15 pmole per original culture.

The following example is illustrative but not limiting of the embodiments of the present invention.

EXAMPLE 1

Preparation of 2,4-bis-(1-Adamantyl)phenol.

Activated silica was prepared by heating Silica Gel 60 (EM Industries) in a flask under high vacuum at 180 °C for 12 h. and was stored under an argon atmosphere. A stirred

suspension of activated silica (1.5g) 1-adamantyl bromide (2.6 g, 12 mmol) and anhydrous phenol (188 mg, 2 mmol), in dry carbon tetrachloride was heated at reflux under an argon atmosphere for 18 h. Another portion of activated silica (0.43 g) was added and the mixture refluxed another 18 h. The resulting mixture was filtered on a Buchner funnel, the solid rinsed with methylene chloride, and the chilled filtrate neutralized with chilled sodium carbonate solution. The organic phase was dried over anhydrous sodium carbonate, filtered, and concentrated *in vacuo*. The residue was chromatographed (silica gel; chloroform: cyclohexane; 1:2), and the pure fractions combined and concentrated to afford the titled compound as a white solid (29% yield, 210 mg), mp 202-203 °C.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

EXAMPLE 2

Inhalant Formulation

The present compound is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

EXAMPLE 3

Tablet Formulation

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Present compound)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

EXAMPLE 4

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of the present compound in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A method of modulating a cannabinoid receptor which comprises administering to a subject in need thereof, an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

2. A method of treating an immunologically-mediated inflammatory disease selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple sclerosis, diabetes and thyroiditis which comprises administering to a subject in need thereof an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

3. A method of treating a disease selected from the group consisting of ankylosing spondylitis, gout, gouty arthritis, osteoarthritis and osteoporosis which comprises administering to a subject in need thereof an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

4. A method of treating renal ischemia which comprises administering to a subject in need thereof an effective amount of 2,4-bis-(1-adamantyl)phenol or a pharmaceutically acceptable salt thereof.

5. A method of treating brain trauma due to edema resulting from cranial injury which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24803

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/045
US CL :514/729

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/729

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, HCAPLUS, USPATFULL- compound of claims for any therapeutic purpose.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ONG, S.H. Adamantyl-substituted phenols. J. Chem. Soc. D. 1970, Vol. 18, page 1180.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search 28 JANUARY 1999	Date of mailing of the international search report 26 FEB 1999
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